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Systematic Review in Clinical Medicine

Intra-articular versus intravenous tranexamic acid in total hip arthroplasty: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Introduction: Given the increasing prevalence of hip dysfunction and the consequent rise in total hip arthroplasty procedures, our research aims to elucidate the optimal administration route of tranexamic acid to minimize perioperative complications and enhance patient.

Methods: The BioMedCentral, PubMed, EMBASE, Scopus, and Cochrane Central Register databases were searched for pertinent studies published up until January 12, 2024. Randomized and quasi-randomized clinical trials comparing intravenous versus intra-articular tranexamic acid in adult patients under total hip arthroplasty were included. Pooled analysis was conducted using Review Manager v. 5.4 software (RevMan). The level of statistical significance was set at $p < 0.05$.

Results: Nineteen trials were included in the meta-analysis. Hemoglobin drops after IV-TXA compared to IA-TXA showed no statistically significant differences (SMD = -0.08; 95%CI: -0.41 to 0.24; p=0.61). The situation was similar for hemoglobin drop (SMD = 0.03; 95%CI: -0.10 to 0.17; p=0.62). Total blood loss for IV-TXA was 935 ± 527 mL, compared to 962 ± 519 mL for IA-TXA (SMD = -0.07; 95%CI: -0.19 to 0.05; p=0.23; Figure 6). The need for blood transfusion was noted in 8.1% of IV-TXA-treated patients and 8.3% of IA-TXA-treated patients (OR = 0.95; 95%CI: 0.66 to 1.38; p=0.79).

Discussion and Conclusions: Both the intravenous and intra-articular tranexamic acid administration showed the same level of effectiveness in limiting blood loss, lowering post-operative complications, and minimizing overall adverse events in total hip arthroplasty. These approaches may be used interchangeably at the clinician's discretion without determining the superiority of any method. Moreover, it is vital to include tranexamic acid in the guidelines since it should be frequently used in any operation of this kind.

Take-home message: Both intravenous and intra-articular tranexamic acid administration in total hip arthroplasty are equally effective in reducing blood loss, minimizing post-operative complications, and decreasing overall adverse events. Clinicians can use either method based on individual patient factors without a significant difference in outcomes.
Keywords: intra-articular; intravenous; tranexamic acid; topical; total hip arthroplasty.

INTRODUCTION

Hip dysfunction, encompassing a range of conditions such as osteoarthritis (OA), rheumatoid arthritis, and traumatic injuries, represents a significant public health concern due to its prevalence and impact on quality of life [1, 2]. For example, the incidence of hip osteoarthritis is increasing in parallel with the aging global population. The Prevalence Trends of Site-Specific OA from the Global Burden of Disease Study 2019 revealed that the number of people affected by arthritis significantly rose by 113.25% over a span of 10 years. Specifically, the prevalence of OA grew from 247.51 million cases in 1990 to 527.81 million cases in 2019 [3,4]. This degenerative joint disease is a leading cause of hip dysfunction, contributing to pain, stiffness, and reduced mobility in affected individuals [5].

Total hip arthroplasty has become a cornerstone in the management of severe hip dysfunction, particularly in elderly populations. Due to factors like an aging population, improvements in surgical methods, and higher patient expectations for maintaining an active lifestyle, the frequency of THA procedures has been increasing. According to recent epidemiological studies, the demand for THA is projected to continue to grow in the coming decades, highlighting its significance as a major orthopedic intervention [6]. This increasing trend in THA surgeries underscores the importance of addressing associated complications, such as perioperative bleeding. Transfusing blood is often required during THA procedures because to significant blood loss, which has inherent risks. Previous studies have shown that the total amount of blood lost during the perioperative phase of THA may reach up to 1500 mL, and around 20% of patients may need a blood transfusion [7]. Perioperative total blood loss refers to the combined volume of blood lost during surgery that is observable, as well as the blood lost by drainage following the procedure. Additionally, it encompasses the phenomenon referred to as hidden blood loss. Hidden blood loss refers to the unmeasurable amount of blood lost during the perioperative period, regardless of the visible blood loss and the volume of blood drained after surgery [8]. An excessive amount of hidden blood loss may exacerbate post-operative anemia, hence increasing the probability of wound disruption, infection, disorientation, and other complications [9]. Utilizing effective hemostatic therapies during the perioperative period might reduce the need for blood transfusions, save valuable blood resources, lower the incidence of transfusion-related diseases and adverse reactions, and control hospital expenses [10]. As THA becomes more commonplace, the need for effective and safe strategies to manage this complication becomes more pressing, further emphasizing the relevance of investigating the optimal use of interventions like tranexamic acid (TXA).

TXA, an antifibrinolytic agent, has become increasingly pivotal in managing perioperative bleeding associated with THA. TXA exerts its effect primarily by inhibiting plasminogen activation and plasmin activity. Plasmin, a key enzyme in the

fibrinolysis process, is responsible for breaking down fibrin clots. By inhibiting plasminogen and plasmin, TXA reduces the breakdown of fibrin clots, thereby stabilizing clot formation and diminishing overall blood loss [11]. The clinical implications of TXA's action are significant in the context of THA. It has been extensively studied and demonstrated to reduce blood loss and the subsequent need for blood transfusions effectively. These outcomes are crucial, as they directly correlate with a reduced risk of transfusion-related complications, shorter hospital stays, and quicker patient recovery times [12].

However, the method of TXA administration during THA remains a subject of ongoing research and debate. The efficacy and safety of intravenous (IV) versus intraarticular (IA) administration are particularly under scrutiny. IV administration delivers TXA systemically, providing widespread antifibrinolytic effects throughout the body. In contrast, IA administration allows for direct delivery of TXA to the joint space, potentially increasing its concentration at the surgical site while minimizing systemic exposure [13,14]. This distinction is particularly relevant for patients with specific comorbidities, where systemic administration might pose higher risks. Recent studies, including randomized controlled trials and meta-analyses, have provided insights but not conclusive evidence favoring one route over the other. For instance, Gómez-Aparicio et al. conducted a randomized controlled trial comparing the effects of IV and IA TXA in THA, focusing on parameters like post-operative hemoglobin drop, total blood loss, and transfusion requirements [15]. Their findings suggested no significant differences between the routes in reducing post-operative bleeding or transfusion needs but raised questions about the possible variances in efficacy based on patient age and other demographic factors. This distinction in administration routes is important not only because of their different effects on bleeding control but also because of their various safety profiles, particularly in patients with pre-existing medical conditions that systemic antifibrinolytic therapy may make worse.

This article aims to delve into the nuances of IV versus IA TXA administration in THA, examining the latest research and synthesizing findings from various studies. By comparing outcomes, safety profiles, and specific patient considerations, we aim to provide a comprehensive overview that can guide clinicians in optimizing TXA use in THA and contribute to the ongoing discourse in orthopedic surgery.

METHODS

This meta-analysis follows the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16]. The study protocol was developed a priori and was not subject to modification during the study. A protocol for this meta-analysis has not been registered. Our study did not require ethical approval.

Eligibility criteria

Inclusion criteria contemplated studies (1) prospective, randomized, and quasi-randomized controlled trials; (2) in English or Spanish; (3) performed in adults (≥ 18 years old); (4) comparing intravenous versus intra-articular tranexamic acid under total hip arthroplasty; (5) indicating outcomes including total blood loss, hematocrit or hemoglobin drop, the need for transfusions. Exclusions were made for studies that did not meet these inclusion criteria and for review articles, case reports, and abstracts. When multiple publications reported on the same or overlapping patient groups, only the most recent publication or the one providing the most comprehensive data was selected. The authors resolved any differences in opinion through a consensus discussion.

Information sources and search strategies

BioMedCentral, PubMed, EMBASE, Scopus, and the Cochrane Central Register databases were searched for potentially eligible trials from inception to 12 January 2024. We have limited articles to articles published in English and Spanish language. References of the previously published meta-analyses were also searched for eligible trials. The search strategy included pre-defined search terms related to TXA and total hip arthroplasty, namely, "tranexamic acid" OR "tranexam" OR "TXA" AND "total hip arthroplasty" OR "THA" OR "hip replacement" OR "hip arthroplasty" OR "randomized

controlled trial" OR "randomized clinical trial" OR "RCT". Duplicates between the different databases were removed.

Study selection

Two authors (JP and MAJ) independently searched the title and abstract of the potentially eligible articles. Finally, the full text of the possible articles was retrieved and assessed for eligibility. Any disputes between the two authors were solved by discussion and consultation with a third author (LS).

Data extraction

Data extraction process was performed by two independent review authors (JP and MP). Any disagreement between the two independent reviewers, at any of the study phases, was solved by discussion with involvement of a third reviewer (LS). Relevant data from included articles were extracted by a pair of independent authors (FC, GN) into a structured proforma. Another author crosschecked these data before analysis (KK).

Risk of bias assessment

The internal validity and risk of bias of included trials were appraised according to The Cochrane Collaboration methods [17] by two independent reviewers (JP and MAJ), with divergences resolved by discussion with third reviewer (MP). We made comparisons of data regarding studies, results, study methodology, design strengths and weaknesses. In each case, we evaluated the risk of bias using the Rob2 tool for randomized [18]. The Rob2 tool includes the following criteria: randomization process, deviations from intended intervention, missing outcome data, measurement of the outcome, and selection of the reported result. To visualize the risk of bias assessments, we used the RobVis application [19].

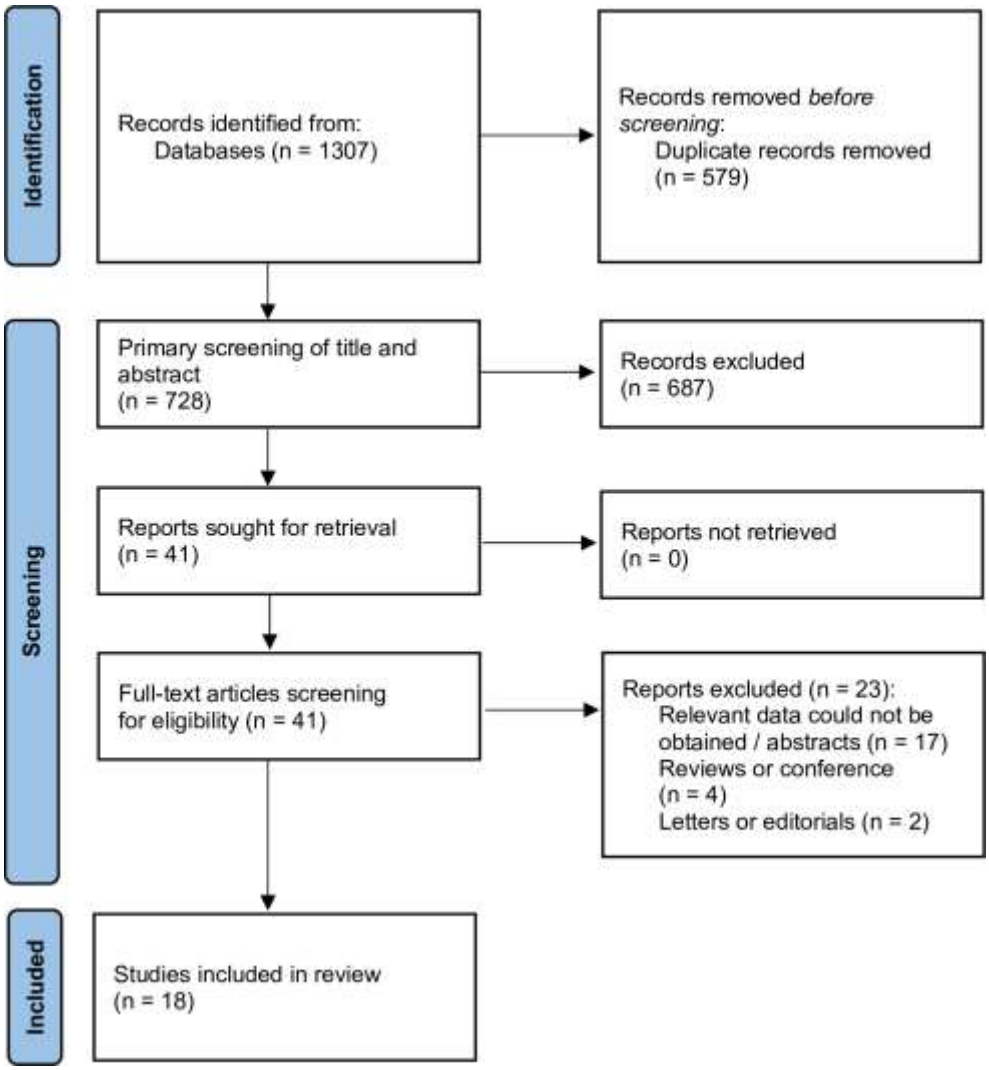
Statistical analysis

The statistical analysis was performed using RevMan 5.4. Software (Review Manager, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). For dichotomous outcomes, the authors calculated individual and pooled risk ratios with 95% confidence intervals (CI). For continuous variables, the mean difference (MD) or standardized mean difference (SMD) with a corresponding 95% CI was calculated. In situations where continuous outcomes in a study were presented as median, range, and interquartile range, means and standard deviations were calculated using the method proposed by Hozo and colleagues [20]. All analyses employed a random-effects model. The extent of heterogeneity was quantitatively determined using the I^2 statistic, with an I^2 value $< 25\%$ indicating low heterogeneity, 25–50% suggesting moderate heterogeneity, and $> 50\%$ indicating high heterogeneity [21]. To identify potential bias, Egger's test and funnel plots were used, and in cases where a single meta-analysis included more than ten trials, tests for funnel plot asymmetry were conducted to evaluate possible publication bias. Finally, in sensitivity analyses, leave-one-out analysis was performed.

RESULTS

The results of the literature search and study selection process are outlined in the PRISMA flow chart (Fig. 1). A total of 1307 studies were identified from BioMed Central, PubMed, EMBASE, Scopus and the Cochrane Central Register databases. Consequently, only 728 studies remained after removing unnecessary and repetitive studies and those carried out in languages other than English or Spanish. After removing repetitions, the abstracts and titles of the remaining 728 studies were examined. Furthermore, the full texts of 41 studies were screened for qualifications and evaluated according to the inclusion criteria. After applying the inclusion and exclusion criteria, nineteen RCTs with a total of 2089 subjects were included in this review [15, 22-38].

Figure 1. PRISMA checklist.



Study characteristics

The clinical characteristics of all the included RCTs are illustrated in Table 1. Each trial included between 50 and 203 THA surgery patients. The articles analyzed in this meta-analysis were published between 2014 and 2023. Of the 19 trials, nine were performed in China [24,27,31,33–38], two were performed in Spain [15,22], one was performed in Australia [23], Slovakia [25], Greece [26], USA [28], Turkey [29], Bosnia and Herzegovina [30] and Belgium [32]. All included trials had a low risk of bias (Figures 2 and 3).

Mean age of patients treated with IV-TXA and IA-TXA was 64.6 ± 10.3 and 64.3 ± 10.8 years, respectively (MD = 0.41; 95%CI: -0.54 to 1.36; p=0.40). BMI in the group of patients treated with IV-TXA was 25.2 ± 4.6 while in the IA-TXA group it was 25.3 ± 4.7(MD = -0.06; 95%CI: -0.16 to 0.03; p=0.18). In the IV-TXA and IA-TXA groups, men constituted respectively: 44.7% vs. 44.1% (OR = 1.04; 95%CI: 0.87 to 1.24).

Table 1. Baseline characteristics of included trials.

Study	Country	Study design	IV-TXA				IA-TXA			
			No.	Age	Sex, male	BMI	No.	Age	Sex, male	BMI
Gómez-Aparicio et al., 2020	Spain	RCT	110	63.9 (10.8)	48 (43.6%)	28.3 (3.8)	85	65.5 (10.9)	45 (52.9%)	29.2 (5.3)
Gómez Barbero et al., 2018	Spain	RCT	31	62.74 (11.95)	28	28.52 (3.98)	47	63.4 (12.51)	25	28.44 (3.91)
Hasan et al., 2021	Australia	RCT	35	70.0 (10.2)	14	27.7 (5.8)	34	65.2 (10.5)	14	29.1 (6.1)
Jia et al., 2019	China	RCT	60	76.34 (3.55)	27	22.95 (3.81)	60	75.61 (5.27)	33	22.95 (2.21)
Juraj et al., 2021	Slovakia	RCT	41	67.46 (7.12)		NS	41	65.88 (12.29)		NS
Kyriakopoulos et al., 2019	Greece	RCT	41	67.59 (10.15)		NS	41	66.14 (11.49)		NS
Luo et al., 2017	China	RCT	60	66.98 (8.57)	27	24.51 (3.87)	60	64.42 (8.02)	25 (13.9%)	25.57 (4.19)
North et al., 2016	USA	RCT	70	64.1 (12.0)	38	31.1 (5.4)	69	65.7 (10.6)	39	31.1 (6.4)
Örs et al., 2021	Turkey	RCT	30	54.1 (12.3)	13	28.2 (4.1)	41	50.3 (11.8)	13	27.3 (4.3)
Palija et al., 2020	Bosnia and Herzegovina	RCT	40	62.88 (7.13)	19 (47.5%)	30.2 (4.88)	40	59.88 (10.25)	13 (32.5%)	29.26 (4.46)
Shen et al., 2023	China	RCT	82	67.63 (5.1)	40	21.81 (2.45)	79	67.09 (4.69)	42	22.16 (2.22)
Vies et al., 2021	Belgium	RCT	60	61.5 (11.8)	29	27.6 (4.4)	60	64.0 (13.4)	22	26.3 (4.4)
Wei et al., 2014	China	RCT	101	63.6 (7.0)	NS	24.2 (3.1)	102	60.2 (6.5)	NS	25.3 (3.0)
Xie et al., 2016	China	RCT	70	59.53 (11.5)	20	24.16 (3.08)	70	62.24 (11.04)	25	24.47 (3.3)
Xu et al., 2019	China	RCT	68	62.5 (6.6)	32	22.0 (2.3)	72	61.9 (6.1)	34	22.3 (2.7)
Zhang et al., 2016	China	RCT	25	44.5 (2.4)	14	24.3 (3.2)	25	44.3 (3.7)	13	23.5 (3.4)
Zhou et al., 2018	China	RCT	56	65.8 (9.4)	17	23.2 (3.1)	57	63.2 (10.0)	12	23.7 (3.2)

Zhou et al., 2023	China	RCT	42	64.86 (9.67)	20	21.81 (2.8)	84	67.17 (10.02)	44	22.23 (2.72)

Figure 2. A summary table of review authors' judgements for each risk of bias item for randomized study.

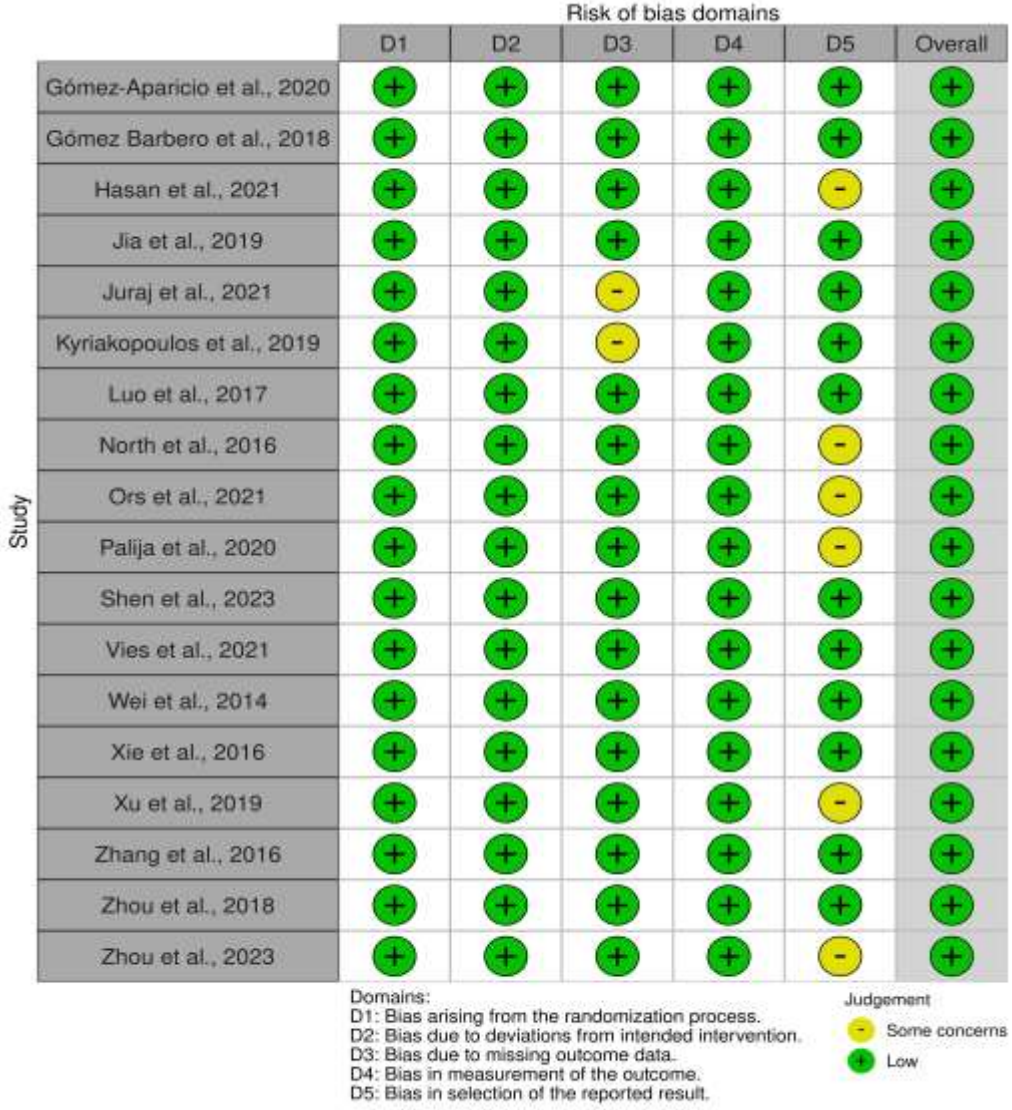
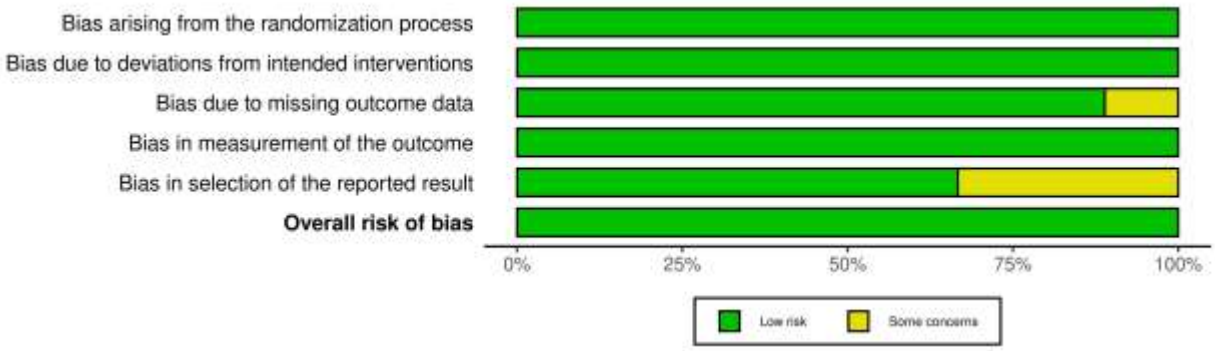


Figure 3. A plot of the distribution of review authors' judgements across non randomized studies for each risk of bias item.



Outcomes

Hemoglobin drops after IV-TXA compared to IA-TXA showed no statistically significant differences (SMD = -0.08; 95%CI: -0.41 to 0.24; p=0.61; Figure 4). The situation was similar for hemoglobin drop (SMD = 0.03; 95%CI: -0.10 to 0.17; p=0.62; Figure 5). Total blood loss for IV-TXA was 935 ± 527 mL, compared to 962 ± 519 mL for IA-TXA (SMD = -0.07; 95%CI: -0.19 to 0.05; p=0.23; Figure 6).

The need for blood transfusion was noted in 8.1% of IV-TXA-treated patients and 8.3% of IA-TXA-treated patients (OR = 0.95; 95%CI: 0.66 to 1.38; p=0.79; Figure 7). The mode of administration of TXA, by IV or IA route also did not affect the length of the hospital stay, which was the respective 4.5 ± 1.5 vs. 4.6 ± 1.5 days (SMD -0.04; 95%CI: -0.18 to 0.11; p=0.60; Figure 8).

Figure 4. Forest plot of hemoglobin drop among IV-TXA vs. IA-TXA patients. The center of each square represents the stanarized mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results.

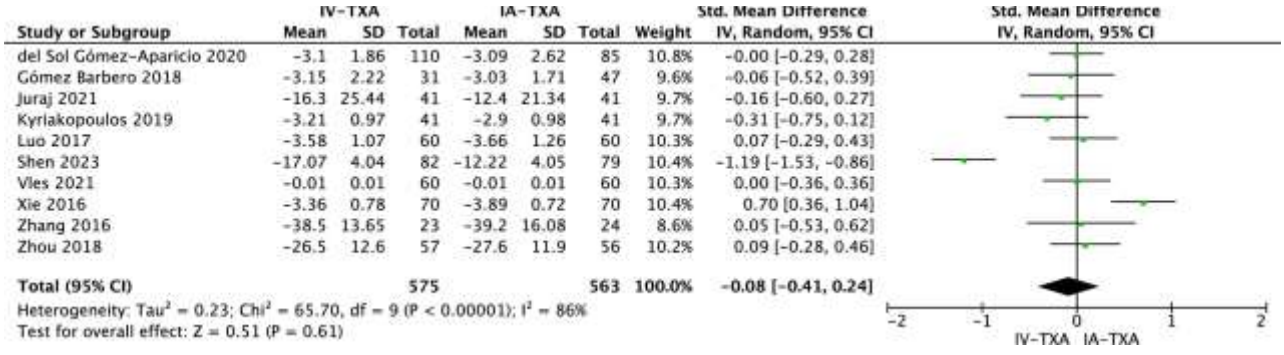


Figure 5. Forest plot of hematocrit drop among IV-TXA vs. IA-TXA patients. The center of each square represents the stanarized mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results.

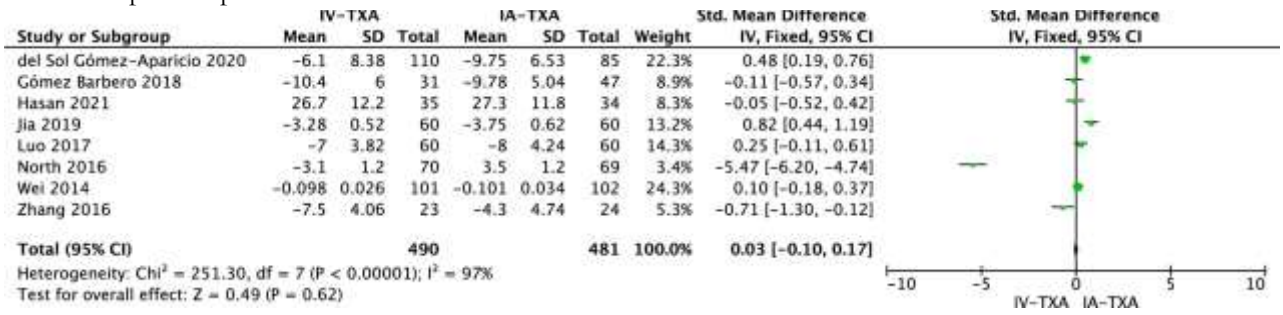


Figure 6. Forest plot of total blood loss among IV-TXA vs. IA-TXA patients. The center of each square represents the stanarized mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results.

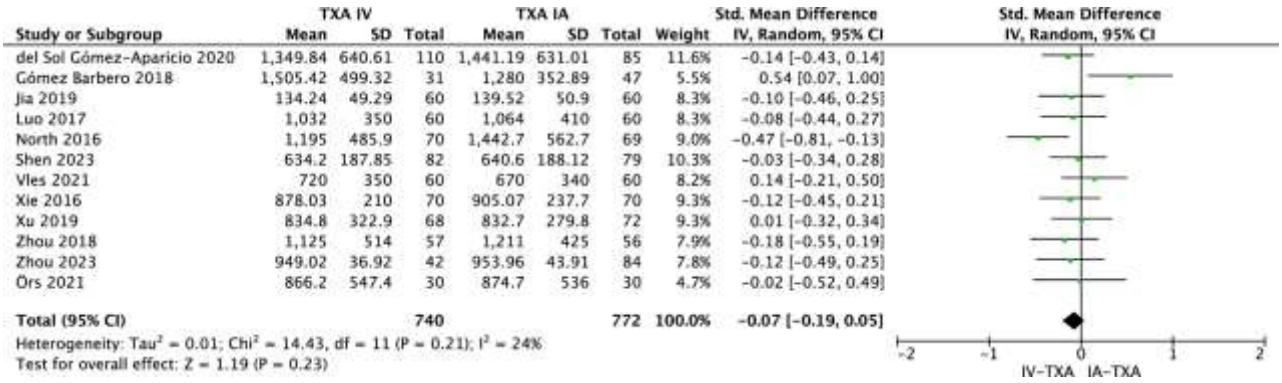


Figure 7. Forest plot of transfusion rate among IV-TXA vs. IA-TXA patients. The center of each square represents the odds ratios for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results.

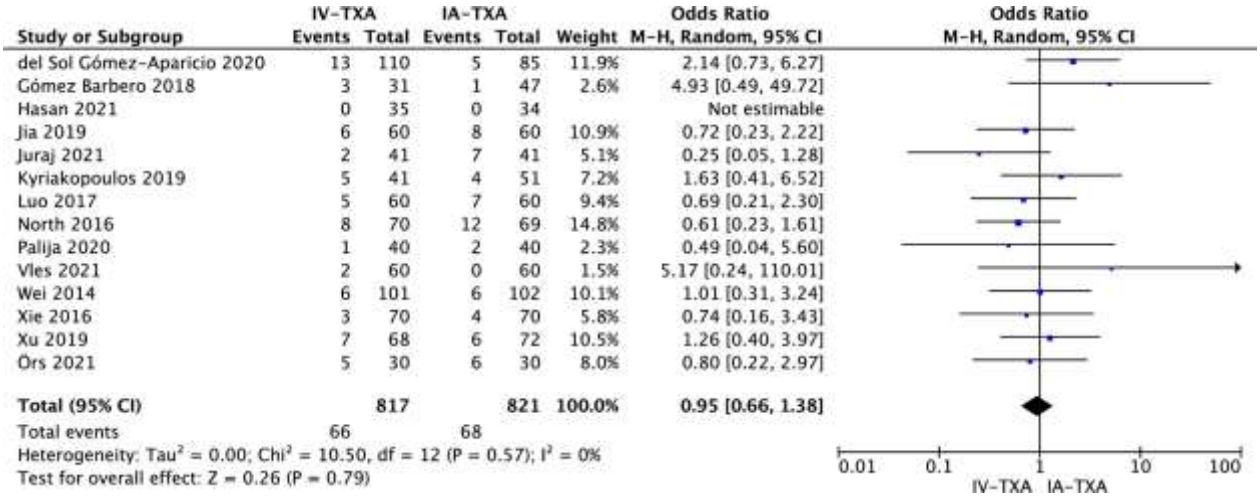
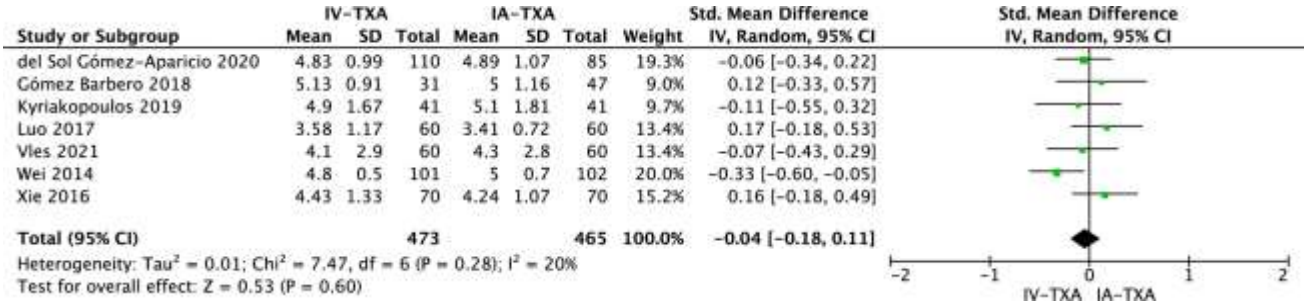


Figure 8. Forest plot of lenght of hospital stay among IV-TXA vs. IA-TXA patients. The center of each square represents the stanarized mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results.



There were no significant differences in the incidence of complications between IV-TXA and IA-TXA. Pooled analysis of complications is shown in Table 2.

Table 2. Pooled analysis of analyzed complications.

Adverse event	No of studies	Event / Participants		Events		Heterogeneity between Trials		p-Value for Differencess across Groups
		IV-TXA	IA-TXA	OR	95%CI	p-value	I² statistics	
DVT	5	2/334 (0.6%)	2/338 (0.6%)	1.02	0.18 to 5.95	0.65	0%	0.98
PE	5	1/381 (0.3%)	0/383 (0.0%)	3.22	0.13 to 80.46	NA	NA	0.48
Cardiac infarction	2	0/130 (0.0%)	0/130 (0.0%)	NE	NE	NA	NA	NA
Stroke	2	0/130 (0.0%)	0/130 (0.0%)	NE	NE	NA	NA	NA
Acute renal failure	2	0/130 (0.0%)	0/130 (0.0%)	NE	NE	NA	NA	NA
Wound renal failure	4	14/299 (4.7%)	18/304 (5.9%)	0.76	0.37 to 1.59	0.66	0%	0.47

Note: CI: confidence interval; DVT: deep veint thrombosis; OR: odds ratio; PE: pulmonary embolism

DISCUSSION

Tranexamic acid has become a pivotal agent in the management of perioperative blood loss in orthopedic surgeries. Its role in reducing blood loss and minimizing the need for transfusions is well-documented, as evidenced by a plethora of studies conducted over recent years [39]. Surgical procedures, particularly those as invasive as THA, pose a significant risk of blood loss, which can lead to various post-operative complications, including prolonged recovery time, increased risk of infections, and the need for blood transfusions [40]. TXA has shown remarkable efficacy in mitigating these risks. This is particularly vital in THA, where blood preservation is crucial for patient recovery and overall surgical success.

The present meta-analysis showed that the comparison between intravenous (IV-TXA) and intra-articular (IA-TXA) routes reveals no statistically significant difference in the drop of hemoglobin levels post-surgery. Further, the total blood

loss associated with IV-TXA was 935 ± 527 mL compared to 962 ± 519 mL for IA-TXA. This marginal difference, represented by an SMD of -0.07 (95% CI: -0.19 to 0.05; p=0.23), suggests that both routes are almost equally effective in controlling blood loss. Regarding the need for blood transfusions, the rates were closely aligned, with 8.1% in the IV-TXA group and 8.3% in the IA-TXA group (OR = 0.95; 95% CI: 0.66 to 1.38; p=0.79). This further supports the argument that both routes are comparably effective. Additionally, the mode of TXA administration did not significantly influence the length of hospital stay, which was similar for both groups (4.5 ± 1.5 days for IV-TXA vs. 4.6 ± 1.5 days for IA-TXA; SMD -0.04; 95% CI: -0.18 to 0.11; p=0.60). Most importantly, the incidence of complications did not differ significantly between the IV-TXA and IA-TXA groups, as confirmed by a pooled analysis of complications. In examining the routes of TXA administration, several studies have compared the effectiveness of IV and topical applications. Intravenous administration of TXA has been the more traditional approach and is known for its systemic effects. Topical administration directly at the surgical site offers the potential benefits of localized action with reduced systemic exposure. This method has gained attention for its efficacy in reducing blood loss while potentially minimizing systemic risks. The safety profile of TXA, particularly in terms of thrombotic risk, has been a topic of considerable interest and investigation. TXA, by its mechanism of action, could theoretically increase the risk of thrombosis. However, current evidence from numerous studies suggests that TXA, irrespective of the route of administration, does not significantly elevate the risk of thrombotic events [41]. This has been a reassuring finding for clinicians and patients alike, as it widens the scope of TXA's applicability in THA without adding substantial risk. This equivalence in safety profile is critical for clinical decision-making, offering flexibility in choosing the administration route based on patient-specific factors and surgical protocols. Overall, these findings underscore the versatility and efficacy of TXA in surgical blood management, regardless of the route of administration.

In our analysis, we included all the available randomized controlled trials, distinguishing it from previous meta-analyses. Furthermore, we acquired a more extensive sample size and a higher quantity of randomized trials in comparison to the previously published meta-analysis. This suggests that our study has a higher level of statistical power. Nevertheless, the analysis included some qualitative limitations specifically related to the randomized controlled trials that were included. The blood transfusion technique exhibits variability across hospitals, and the decision to provide a blood transfusion is contingent upon the subjective evaluation of the attending healthcare professionals. The variety in the duration of operation, the approach used, access type, and the means of obtaining data in the research may have an influence on the outcomes. Moreover, the use of distinct anesthetic techniques may impact the extent of bleeding experienced during surgical operations and the need for blood transfusion.

CONCLUSIONS

Both the intravenous and intra-articular methods of administering tranexamic acid showed the same level of effectiveness in limiting blood loss, lowering post-operative complications, and minimizing overall adverse events in total hip arthroplasty. These approaches may be used interchangeably at the clinician's discretion, without needing to determine the superiority of any one method. Moreover, it is vital to include tranexamic acid in the guidelines, since it should be frequently used in any operation of this kind.

Author Contributions: Conceptualization: J.P.; methodology: J.P. and L.S; software: L.S.; validation: J.P.; formal analysis, J.P. and L.S.; investigation: J.P., M.A-J., G.N., M.P., K.K. and L.S.; resources: J.P. and L.S.; data curation: J.P.; writing—original draft preparation: J.P., M.P. and L.S.; writing—review and editing, J.P., F.C., M.P., G.N., K.K., L.S. and M.A-J.; visualization: J.P.; supervision: L.S. and M.A-J.; project administration: J.P.. All authors have read and agreed to the published version of the manuscript.

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